

CLAIMS

1. A method for the treatment of non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising the repeated administration over an extended period of time of a compound with prolonged action after each administration, said prolonged action necessary to achieve sustained glycemic control in mammals, said compound selected from the group consisting of:

(a) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

(b) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)

wherein X is selected from the group consisting of:

(A) Lys,

(B) Lys-Gly, and

(C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure



wherein W is an amino acid sequence selected from the group consisting of

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Gly-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 1) and

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Gly-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 6)

which derivative when processed in a mammal results in a polypeptide derivative having an insulinotropic activity;

(d) a derivative of a polypeptide comprising the primary structure



wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Gly-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg; (SEQUENCE ID NO: 3)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly; (SEQUENCE ID NO: 4) and

5 His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys; (SEQUENCE ID NO: 5)

and

(e) a derivative of said peptides (a) through (d) wherein said derivative is  
selected from the group consisting of:

- 10 (1) a pharmaceutically acceptable acid addition salt of said peptides;  
(2) a pharmaceutically acceptable carboxylate salt of said peptides;  
(3) a pharmaceutically acceptable alkali addition salt of said peptides;  
(4) a pharmaceutically acceptable lower alkyl ester of said peptides; and  
(5) a pharmaceutically acceptable amide of said peptides wherein said

15 pharmaceutically acceptable amide is selected from the group consisting of amide,  
lower alkyl amide and lower dialkyl amide.

2. The method of claim 1 wherein said administration is subcutaneous.

3. The method of claim 1 wherein said administration is intramuscular.

4. The method of claim 1 wherein said administration is transdermal.

20 5. The method of claim 1 wherein said administration is by an infusion  
pump.

6. The method of claim 1 wherein said administration is by oral inhalation.

7. The method of claim 1 wherein said administration is by nasal inhalation.

8. The method of claim 1 wherein said administration is gastrointestinal.

25 9. A composition of matter comprising;

(i) a compound selected from the group consisting of:

(a) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

30 (b) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)

wherein X is selected from the group consisting of:

- (A) Lys,
- (B) Lys-Gly,
- (C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure

5  $H_2N-W-COOH$

wherein W is an amino acid sequence selected from the group consisting of

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-  
Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly  
(SEQUENCE ID NO: 1) and

10 His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-  
Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg  
(SEQUENCE ID NO: 6)

which derivative when processed in a mammal results in a polypeptide derivative having  
an insulintropic activity;

15 (d) a derivative of a polypeptide comprising the primary structure

$H_2N-R-COOH$

wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 2)

20 His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 3)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly (SEQUENCE ID NO: 4) and

25 His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys; (SEQUENCE ID NO: 5)

a derivative of said peptides (a) through (d) wherein said derivative is selected  
from the group consisting of:

- (1) a pharmaceutically acceptable acid addition salt of said peptides;
- (2) a pharmaceutically acceptable carboxylate salt of said peptides;
- 30 (3) a pharmaceutically acceptable alkali addition salt of said peptides;
- (4) a pharmaceutically acceptable lower alkyl ester of said peptides; and

(5) a pharmaceutically acceptable amide of said peptides wherein said pharmaceutically acceptable amide is selected from the group consisting of amide, lower alkyl amide and lower dialkyl amide, and

(ii) a polymer capable of prolonging the action of said compound to achieve  
5 sustained glycemic control.

10. A composition according to claim 9 wherein said polymer is a low molecular weight polymer.

11. A composition according to claim 9 wherein said polymer is selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, polyvinylalcohol,  
10 polyoxyethylene-polyoxypropylene copolymers, polysaccharides selected from the group consisting of cellulose, cellulose derivatives, chitosan, acacia gum, karaya gum, guar gum, xanthan gum, tragacanth, alginic acid, carrageenan, agarose, and furcellarans, dextran, starch, starch derivatives, hyaluronic acid, polyesters, polyamides, polyanhydrides, and polyortho esters.

15 12. A composition according to claim 11 wherein said polymer is selected from the group consisting of polyethylene glycol and polyvinylpyrrolidone.

13. A composition of matter comprising;

(i) a compound selected from the group consisting of:

(a) a peptide having the amino acid sequence:

20 His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

(b) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)

25 wherein X is selected from the group consisting of:

(A) Lys,

(B) Lys-Gly, and

(C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure

30 
$$\text{H}_2\text{N-W-COOH}$$

wherein W is an amino acid sequence selected from the group consisting of

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-  
Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly  
(SEQUENCE ID NO: 1) and

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-  
5 Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg  
(SEQUENCE ID NO: 6)

which derivative when processed in a mammal results in a polypeptide derivative having  
an insulintropic activity;

(d) a derivative of a polypeptide comprising the primary structure  
10  $H_2N-R-COOH$

wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
15 Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg; (SEQUENCE ID NO: 3)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly; (SEQUENCE ID NO: 4) and

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys; (SEQUENCE ID NO: 5)

20 and

a derivative of said peptides (a) through (d) wherein said derivative is selected  
from the group consisting of:

- (1) a pharmaceutically acceptable acid addition salt of said peptides;
- (2) a pharmaceutically acceptable carboxylate salt of said peptides;
- 25 (3) a pharmaceutically acceptable alkali addition salt of said peptides;
- (4) a pharmaceutically acceptable lower alkyl ester of said peptides; and
- (5) a pharmaceutically acceptable amide of said peptides wherein said  
pharmaceutically acceptable amide is selected from the group consisting of amide,  
lower alkyl amide and lower dialkyl amide, and

30 (ii) a pharmaceutically acceptable water-immiscible oil suspension capable  
of prolonging action of said compound to achieve sustained glycemic control.

14. A composition according to ~~claim~~ 13 wherein said oil is selected from the  
group consisting of peanut oil, sesame oil, almond oil, castor oil, camellia oil, cotton

seed oil, olive oil, corn oil, soy oil, safflower oil, coconut oil, and esters of fatty acids, esters of fatty alcohols.

15. A composition according to claim 13 further comprising a wetting agent.

16. A composition according to claim 15 wherein said wetting agent is a  
5 nonionic surfactant.

17. A composition according to claim 13 further comprising a suspending agent.

18. A composition of matter comprising;

(i) a compound selected from the group consisting of:

10 (a) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

(b) a peptide having the amino acid sequence:

15 His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)

wherein X is selected from the group consisting of:

(A) Lys,

(B) Lys-Gly, and

(C) Lys-Gly-Arg;

20 (c) a derivative of a polypeptide comprising the primary structure



wherein W is an amino acid sequence selected from the group consisting of

25 His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 1) and

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 6)

30 which derivative when processed in a mammal results in a polypeptide derivative having an insulintropic activity;

(d) a derivative of a polypeptide comprising the primary structure



wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 2)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 3)

5 His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly (SEQUENCE ID NO: 4) and

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys (SEQUENCE ID NO: 5);

and

10 a derivative of said peptides (a) through (d) wherein said derivative is selected  
from the group consisting of:

(1) a pharmaceutically acceptable acid addition salt of said peptides;

(2) a pharmaceutically acceptable carboxylate salt of said peptides;

(3) a pharmaceutically acceptable alkali addition salt of said peptides;

15 (4) a pharmaceutically acceptable lower alkyl ester of said peptides; and

(5) a pharmaceutically acceptable amide of said peptides wherein said  
pharmaceutically acceptable amide is selected from the group consisting of amide,  
lower alkyl amide and lower dialkyl amide, and

(ii) zinc (II), which is complexed with the peptide.

20 19. A composition according to claim 18 capable of achieving sustained  
glycemic control.

20. A composition according to claim 18 which is amorphous.

21. A composition according to claim 18 which is crystalline.

22. A composition according to claim 18 which is an aqueous suspension.

25 23. A composition of matter comprising;

(i) a compound selected from the group consisting of:

(a) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

30 (b) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)

wherein X is selected from the group consisting of:

- (A) Lys,
- (B) Lys-Gly, and
- (C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure

5  $H_2N-W-COOH$

wherein W is an amino acid sequence selected from the group consisting of

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-  
Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly  
(SEQUENCE ID NO: 1) and

10 His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-  
Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg  
(SEQUENCE ID NO: 6

which derivative when processed in a mammal results in a polypeptide derivative having  
an insulintropic activity;

15 (d) a derivative of a polypeptide comprising the primary structure

$H_2N-R-COOH$

wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 2)

20 His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 3)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly (SEQUENCE ID NO: 4) and

25 His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys (SEQUENCE ID NO: 5);

and

a derivative of said peptides (a) through (d) wherein said derivative is selected  
from the group consisting of:

- (1) a pharmaceutically acceptable acid addition salt of said peptides;
- 30 (2) a pharmaceutically acceptable carboxylate salt of said peptides;
- (3) a pharmaceutically acceptable alkali addition salt of said peptides;
- (4) a pharmaceutically acceptable lower alkyl ester of said peptides; and



(5) a pharmaceutically acceptable amide of said peptides wherein said pharmaceutically acceptable amide is selected from the group consisting of amide, lower alkyl amide and lower dialkyl amide, and

(ii) a metal selected from the group consisting of Ni (II), Co (II), Mg (II), Ca (II), K (I), Mn (II), Fe(II), and Cu(II).

24. A composition according to claim 23 capable of achieving sustained glycemic control.

25. A composition of matter comprising;

(i) a compound selected from the group consisting of:

(a) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

(b) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)

wherein X is selected from the group consisting of:

(A) Lys,

(B) Lys-Gly, and

(C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure



wherein W is an amino acid sequence selected from the group consisting of

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 1) and

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 6)

which derivative when processed in a mammal results in a polypeptide derivative having an insulintropic activity;

(d) a derivative of a polypeptide comprising the primary structure



wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg; (SEQUENCE ID NO: 3)

5 His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly; (SEQUENCE ID NO: 4) and

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys; (SEQUENCE ID NO: 5)

and

10 a derivative of said peptides (a) through (d) wherein said derivative is selected  
from the group consisting of:

(1) a pharmaceutically acceptable acid addition salt of said peptides;

(2) a pharmaceutically acceptable carboxylate salt of said peptides;

(3) a pharmaceutically acceptable alkali addition salt of said peptides;

15 (4) a pharmaceutically acceptable lower alkyl ester of said peptides; and

(5) a pharmaceutically acceptable amide of said peptides wherein said

pharmaceutically acceptable amide is selected from the group consisting of amide,  
lower alkyl amide and lower dialkyl amide, and

(ii) a basic polypeptide, wherein said composition is an aqueous suspension

20 capable of sustained glycemic control.

26. A composition according to claim 25 wherein said basic polypeptide is  
protamine.

27. A composition of matter comprising;

(i) a compound selected from the group consisting of:

25 (a) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 2);

(b) a peptide having the amino acid sequence:

30 His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)

wherein X is selected from the group consisting of:

(A) Lys,

(B) Lys-Gly,

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(C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure



wherein W is an amino acid sequence selected from the group consisting of

5 His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-  
Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly  
(SEQUENCE ID NO: 1) and

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-  
Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE  
10 ID NO: 6)

which derivative when processed in a mammal results in a polypeptide derivative having  
an insulintropic activity;

(d) a derivative of a polypeptide comprising the primary structure



15 wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 2);

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 3);

20 His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly (SEQUENCE ID NO: 4); and

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys (SEQUENCE ID NO: 5);

and

25 a derivative of said peptides (a) through (d) wherein said derivative is selected  
from the group consisting of:

(1) a pharmaceutically acceptable acid addition salt of said peptides;

(2) a pharmaceutically acceptable carboxylate salt of said peptides;

(3) a pharmaceutically acceptable alkali addition salt of said peptides;

30 (4) a pharmaceutically acceptable lower alkyl ester of said peptides; and

(5) a pharmaceutically acceptable amide of said peptides wherein said

pharmaceutically acceptable amide is selected from the group consisting of amide,  
lower alkyl amide and lower dialkyl amide, and

(ii) a phenolic compound, wherein said composition is an aqueous suspension capable of sustained glycemic control.

28. A composition according to claim 27 wherein said phenolic compound is selected from the group consisting of phenol, cresol, resorcinol, and methyl paraben.

5 29. A composition of matter comprising;

(i) a compound selected from the group consisting of:

(a) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 2);

10 (b) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)

wherein X is selected from the group consisting of:

(A) Lys,

15 (B) Lys-Gly,

(C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure



wherein W is an amino acid sequence selected from the group consisting of

20 His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 1) and

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 6)

25 which derivative when processed in a mammal results in a polypeptide derivative having an insulintropic activity;

(d) a derivative of a polypeptide comprising the primary structure



30 wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 2);

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 3);

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly (SEQUENCE ID NO: 4); and

5 His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys (SEQUENCE ID NO: 5);

and

a derivative of said peptides (a) through (d) wherein said derivative is selected from the group consisting of:

- 10 (1) a pharmaceutically acceptable acid addition salt of said peptides;  
(2) a pharmaceutically acceptable carboxylate salt of said peptides;  
(3) a pharmaceutically acceptable alkali addition salt of said peptides;  
(4) a pharmaceutically acceptable lower alkyl ester of said peptides; and  
(5) a pharmaceutically acceptable amide of said peptides wherein said

15 pharmaceutically acceptable amide is selected from the group consisting of amide, lower alkyl amide and lower dialkyl amide, and

(ii) a basic polypeptide and a phenolic compound, wherein such composition is an aqueous suspension capable of sustained glycemic control.

30. A composition of matter comprising;

20 (i) a compound selected from the group consisting of:

(a) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg; (SEQUENCE ID NO: 2)

(b) a peptide having the amino acid sequence:

25 His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)

wherein X is selected from the group consisting of:

(A) Lys,

(B) Lys-Gly, and

30 (C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure



wherein W is an amino acid sequence selected from the group consisting of

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-  
Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly  
(SEQUENCE ID NO: 1) and

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-  
5 Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg  
(SEQUENCE ID NO: 6)

which derivative when processed in a mammal results in a polypeptide derivative having  
an insulintropic activity;

(d) a derivative of a polypeptide comprising the primary structure

10  $H_2N-R-COOH$

wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
15 Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg; (SEQUENCE ID NO: 3)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly; (SEQUENCE ID NO: 4) and

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys; (SEQUENCE ID NO: 5)

20 and

a derivative of said peptides (a) through (d) wherein said derivative is selected  
from the group consisting of:

- (1) a pharmaceutically acceptable acid addition salt of said peptides;  
(2) a pharmaceutically acceptable carboxylate salt of said peptides;  
25 (3) a pharmaceutically acceptable alkali addition salt of said peptides;  
(4) a pharmaceutically acceptable lower alkyl ester of said peptides; and  
(5) a pharmaceutically acceptable amide of said peptides wherein said  
pharmaceutically acceptable amide is selected from the group consisting of amide,  
lower alkyl amide and lower dialkyl amide, and

30 (ii) a basic polypeptide, a phenolic compound, and a metal ion wherein said  
composition is an aqueous suspension capable of sustained glycemic control.

31. A composition according to claim 30 wherein said basic polypeptide is  
protamine.

32. A composition according to claim 30 wherein said metal ion is zinc.

33. A composition of matter comprising;

(i) a compound selected from the group consisting of:

(a) a peptide having the amino acid sequence:

5 His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 2);

(b) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
10 Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)

wherein X is selected from the group consisting of:

(A) Lys,

(B) Lys-Gly,

(C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure

15  $H_2N-W-COOH$

wherein W is an amino acid sequence selected from the group consisting of

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-  
Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly  
(SEQUENCE ID NO: 1) and

20 His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-  
Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE  
ID NO: 6)

which derivative when processed in a mammal results in a polypeptide derivative having  
an insulintropic activity;

25 (d) a derivative of a polypeptide comprising the primary structure

$H_2N-R-COOH$

wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 2);

30 His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 3);

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly (SEQUENCE ID NO: 4); and

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys (SEQUENCE ID NO: 5);

and

a derivative of said peptides (a) through (d) wherein said derivative is selected

5 from the group consisting of:

- (1) a pharmaceutically acceptable acid addition salt of said peptides;
- (2) a pharmaceutically acceptable carboxylate salt of said peptides;
- (3) a pharmaceutically acceptable alkali addition salt of said peptides;
- (4) a pharmaceutically acceptable lower alkyl ester of said peptides; and

10 (5) a pharmaceutically acceptable amide of said peptides wherein said  
pharmaceutically acceptable amide is selected from the group consisting of amide,  
lower alkyl amide and lower dialkyl amide, and

(ii) said peptides and derivatives thereof having being subjected to  
conditions resulting in amorphous or crystalline material formation.

15 34. A composition according to claim 33 wherein said conditions are high  
shear, exposure to salts; or combinations thereof.

35. A composition according to claim 34 wherein said salt is selected from  
the group consisting of ammonium sulfate, sodium sulfate, lithium sulfate, lithium  
chloride, sodium citrate, ammonium citrate, sodium phosphate, potassium phosphate,  
20 sodium chloride, potassium chloride, ammonium chloride, sodium acetate, ammonium  
acetate, magnesium sulfate, calcium chloride, ammonium nitrate, and sodium formate;  
and combinations thereof.

36. A composition of matter comprising;

(i) a compound selected from the group consisting of:

25 (a) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

(b) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
30 Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)

wherein X is selected from the group consisting of:

- (A) Lys,
- (B) Lys-Gly, and



(C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure



wherein W is an amino acid sequence selected from the group consisting of

5 His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-  
Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly  
(SEQUENCE ID NO: 1) and

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-  
Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg  
10 (SEQUENCE ID NO: 6)

which derivative when processed in a mammal results in a polypeptide derivative having  
an insulintropic activity;

(d) a derivative of a polypeptide comprising the primary structure



15 wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg; (SEQUENCE ID NO: 3)

20 His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly; (SEQUENCE ID NO: 4) and

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-  
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys; (SEQUENCE ID NO: 5)

and

25 a derivative of said peptides (a) through (d) wherein said derivative is selected  
from the group consisting of:

(1) a pharmaceutically acceptable acid addition salt of said peptides;

(2) a pharmaceutically acceptable carboxylate salt of said peptides;

(3) a pharmaceutically acceptable alkali addition salt of said peptides;

30 (4) a pharmaceutically acceptable lower alkyl ester of said peptides; and

(5) a pharmaceutically acceptable amide of said peptides wherein said

pharmaceutically acceptable amide is selected from the group consisting of amide,  
lower alkyl amide and lower dialkyl amide, and

37. A composition according to claim 36 wherein said liposome is phospholipid based.

39. A method for the treatment of non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising the prolonged administration of a composition according to claim 9.

41. A method for the treatment of non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising of the prolonged administration of a composition according to claim 18.

43. A method for the treatment of non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising of the prolonged administration of a composition according to claim 25.

45. A method for the treatment of non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising of the prolonged administration of a composition according to claim 29.

30 47. A method for the treatment of non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising of the prolonged administration of a composition according to claim 33.

48. A method for the treatment of non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising of the prolonged administration of a composition according to claim 36.

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